Human Subjects Protection at Detrick: Biowarfare to Biodefense

Relationship To Evolution of Regulation by Federal Agencies and Oversight Commissions

Presented By:

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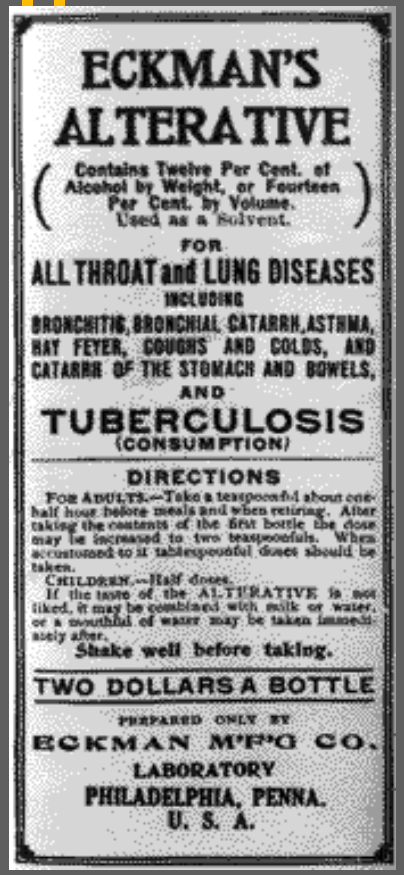
Historic FDA Regulatory Milestones Before World War


ECKMAN'S
ALTERATIVE
Contains Twelve Per Cent. of Alcohol by Weight, or Fourteen Per Cent. by Volume. Used as a Solvent.
FOR
ALL THROAT and LUNG DISEASES
INCLUDING
BRONCHITIS, BRONCHIAL CATARRH, ASTHMA, HAY FEVER, COUGHS AND COLDS, AND CATARRH OF THE STOMACH AND BOWELS,
AND
TUBERCULOSIS
(CONSUMPTION)
DIRECTIONS
FOR ADULTS.—Take a teaspoonful about one-half hour before meals and when retiring. After taking the contents of the first bottle the dose may be increased to two teaspoonfuls. When accustomed to it tablespoonful doses should be taken.
CHILDREN.—Half doses.
If the taste of the ALTERATIVE is not liked, it may be combined with milk or water, or a mouthful of water may be taken immediately after.
Shake well before taking.
TWO DOLLARS A BOTTLE
PREPARED ONLY BY
ECKMAN M'F'G CO.
LABORATORY
PHILADELPHIA, PENNA.
U. S. A.

- **1902 Biologics Control Act.**
  - ensured purity and safety of serums, vaccines, and other biologic products for disease prevention and treatment.
- **1906 Food and Drugs Act.**
  - Regulated label content.
- **1938 Food Drug and Cosmetic Act.**
  - Drugs must be proven safe before marketing, one of new rules.

Human Research Oversight by Office of the Army Surgeon General

- Advisory Commissions Provided 2nd Tier Review:
  - 1900-39 Commissions on YF, Typhoid, Influenza
  - 1939-41 NAS NRC War Bureau Consultants
  - 1942-46 FSA - WRS Committee on Medical Research

Early Human Research Oversight

- **1900** Yellow Fever Commission.
  - First use of “Informed Consent”.
- **1925** Army regulation to promote infectious disease research noted that "volunteers" should be used in "experimental" research.
  - **AR 40-210**, *The Prevention of Communicable Diseases of Man--General* (21 April 1925).
- **1932** the Secretary of the Navy granted permission for:
  - Experiment with divers if they were "informed volunteers“.
- **1938** Food Drug and Cosmetic Act.
  - Drugs must be proven safe before marketing.

U.S Vulnerable To BW As Entry Into WW II Approaches

- U.S. Concerned About The Possibility That The Nazis Were Preparing For BioWarfare.

Pre-WW II: Yellow Fever Plot

- 1939 Japanese scientists attempt to obtain virulent strains of yellow fever virus from the Rockefeller university.
- Attempt thwarted by scientists but information on threat took until 1941 to reach War Department.

U.S. Unprepared for BW in WWII

1941 - Secretary of War Henry L. Stimson wrote to Frank B. Jewett, president of the National Academy of Sciences and asked him to appoint a committee to recommend actions:

“Because of the dangers that might confront this country from potential enemies employing what may be broadly described as biological warfare, it seems advisable that investigations be initiated to survey the present situation and the future possibilities.”

Dr. Edwin B. Fred (NAS) - War Bureau of Consultants (WBC).

WBC Committee Concludes Biological Warfare a Possibility

WBC Committee reports to Secretary Stimson:

“There is but one logical course to pursue, namely, to study the possibilities of such warfare from every angle, make every preparation for reducing its effectiveness, and thereby reduce the likelihood of its use.”

The War Reserve Service (WRS) was established, under George W. Merck, inside the Civilian Federal Security Agency (FSA) to begin development of the US Biological Warfare program with offensive and defensive objectives.

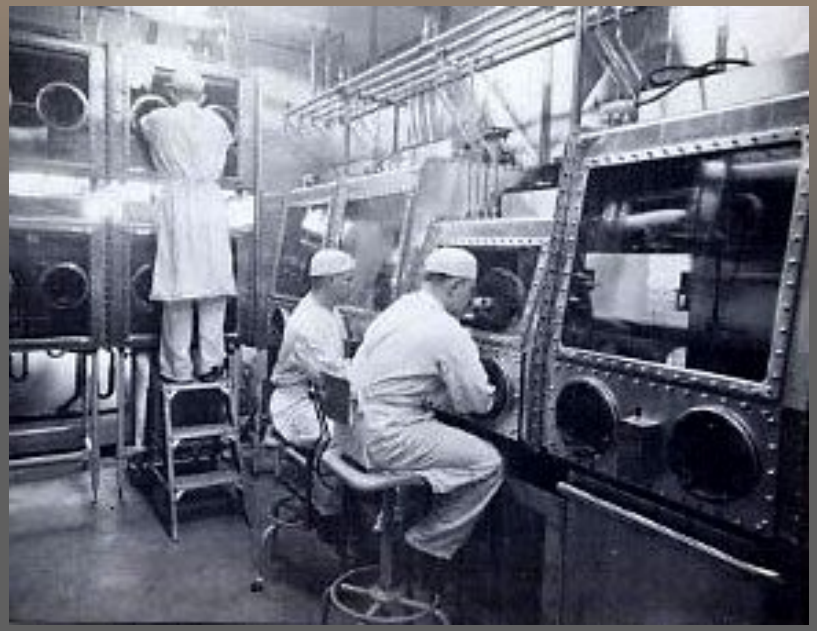
War Reserve Service -WRS

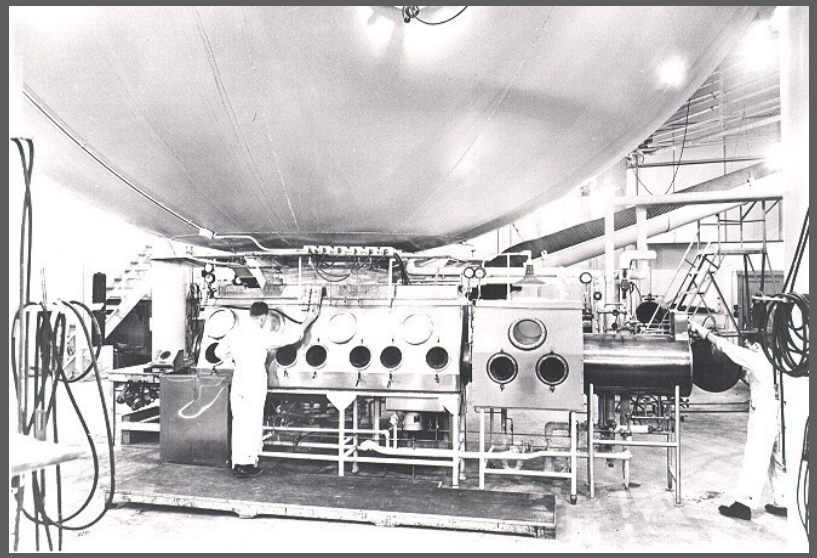
- First Major Objective of WRS was to develop defensive measures against possible BW attack.
- WRS Organized a research and development program within the War Department in 1942 that became RDTE.
- Chemical Warfare Service of the Army commenced operation of large scale R&D program in Nov 1942.
- CWS Constructed laboratories and pilot plants.
- First Facility at Camp Detrick started April 1943.

Detrick Field Was An Air National Guard Training Center

It Became A Bio- Warfare Center as Camp Detrick

Camp Detrick developed biosafety before it produced biowarfare





Civilian Human Subjects Research 1943-1946 Supported by WRS-CMR

- The Federal Security Agency issued grants to civilian medical researchers at universities, companies and research institutes after review by WRS Committee on Medical Research - CMR.
- A list of persons directing specific contract protocols included eminent scientists, future Nobel prize winners and corporate leaders who shaped modern biology, pharmaceuticals and medicine.

1942 WRS-CMR
Use of Human Research Subjects

- On 9 Oct 1942, the Chairman's general statement was endorsed by the full committee:
- "Human experimentation is not only desirable, but necessary in the study of many of the problems of war medicine which confront us. When any risks are involved, volunteers only should be utilized as subjects, and these only after the risks have been fully explained and after signed statements have been obtained which shall prove that the volunteer offered his services with full knowledge and that claims for damage will be waived. An accurate record should be kept of the terms in which the risks involved were described."

Re: WRS-CMR Statement on Use of Human Research Subjects- 1942

- Despite WRS-CMR's statement, it supported other experiments performed by civilian scientists that involved subjects whose capacity to give valid consent to participation was doubtful, including institutionalized people with cognitive disabilities.
- Several immoral WRS studies made it into the newspapers and were referred to by the attorneys who defended Nazi physicians in Nuremberg.

WW II "Human Experimentation" In Camp Detrick Safety Practices

- 1st Objective of Immunization*:
  - Vaccination routine called "special procedures" instituted by Biological Protection Branch of S Division primarily to protect workers.
- 2nd Objective was to:
  - Determine most efficacious immunization methods.
  - Determine effectiveness of available preparations.
  - Only vaccines available were experimental.

* Sp Rpt 15, Immunological Protection of Personnel Against B.W. Agents (Oct 46), p.2.

WW II "Human Experimentation" In Camp Detrick Safety Practices

- Permission to use experimental vaccines in humans required from Surgeon Generals of Army and Navy before unproved Materials used.
  - Personnel underwent medical examination upon assignment to Camp Detrick and initial blood samples were saved for later comparison.
  - Chronological records kept for each person of blood samples taken, injections, skin tests given, and titers obtained and exposures monitored.

WW II "Human Experimentation" In Camp Detrick Safety Practices

- The first candidate vaccines used to protect workers came from WRS directors and AEB consultants located in universities and institutes all over the United States.
- First Vaccinations (selected examples):
  - First Anthrax Vaccine was a killed vegetative whole cell vaccine (*authorized November 1943*).
    - It was given to 205 persons, but stopped July 1944 because there was no evidence of animal protection or serological response.
  - First Botulinum Toxoid Vaccine used in 1943 was a fluid type A toxoid made by Dr. Alwin Pappenheimer (AP321, *Dept Health Lab Jamaica Plain Mass*.*).
    - 0.02 unit per ml determined to be "protective level" for A toxin based on animal surrogate efficacy studies.

WW II “Human Experimentation” In Camp Detrick Safety Practices

- Other worker safety tests were performed to determine effectiveness of air purification systems such as mechanical filters, electrostatic filters, air washers and air incinerators.
- Ambient Air Pressure regulation and other engineering controls were tested.
- Masks and biohazard suits were developed.

WW II - Soldier Deployment: Yellow Fever Vaccine Incident

- A Yellow fever vaccine that was early in development by AEB was given to deploying US troops in January 1942.
- By March 1942 tens of thousands of soldiers had hepatitis and scores died. (WRS-CMR and AEB Investigated).
- The vaccine had been given to protect them against possible biologic attack.
- **1944** Public Health Service Act is passed:
  - regulation of biologics and control of communicable diseases.

WW II - Soldier Deployment: Influenza Vaccine

Memory of the millions of deaths from influenza and pneumonia during World War I haunted the founders of the

- Army Commission determined that the Influenza pandemic of 1918 was amplified by troop movements during World War I.
- Therefore, AEB Commission on Influenza gave an experimental Flu Vaccine to 7 million soldiers deploying for WWII.
- This was a successful venture; and, in 1944, Flu vaccine was approved by the FDA on the strength of Army data.

Camp Detrick After WW II

Military Human Subjects Research Programs at Fort Detrick

- Station Hospital 1943 – 1952
- CD-22 Program 1954 – 1956
- Operation Whitecoat 1956 – 1973
- MRVS Program 1974 – 1998
- Present Clinical Research Program

Human Subjects Research at Camp Detrick 1943 - 1946

The station hospital, activated in 1943, provided a "unique opportunity to study the inception course and therapeutics of many rare diseases in patients whose baseline health data was known"

This was primarily "Opportunist" research that depended upon occupational incidents among workers in the various biowarfare facilities.

Nuremberg Trial - 1947

- The Nuremberg war crimes trials convicted 23 Nazi doctors for murder.
- By 1946 Andrew Ivey released his list of ten conditions required for “permissible medical experiments” in healthy subjects, but code was silent on evaluation of therapeutic drugs in patients suffering from diseases.
- The Nuremberg Code became the standard measure of ethical conduct in military research involving human subjects.

Post WW II BioWarfare Defense

- **1952** Armed Forces Medical Policy Council noted tests with simulants showed U.S. vulnerability to biological attack.
- Extrapolation of animal data to man was opposed.
- Human vulnerability to biological agents was not known.
- Secretary of Army, Army Chief of Staff and Chemical Corps and Army Surgeon General addressed subject of research in defense of biological warfare utilizing human volunteers.
- Ohio State contract, CD-22 and Operation Whitecoat Research Programs for human volunteer studies planned.

Wilson Memorandum of 1953

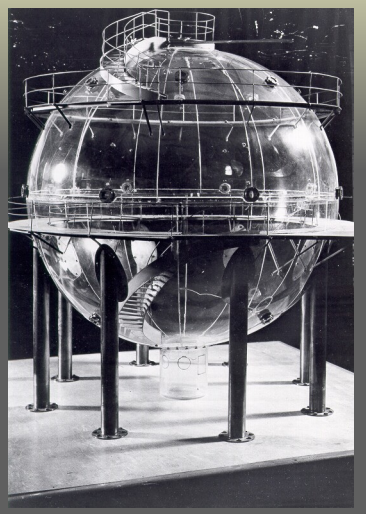
The Nuremberg Code principles were incorporated into the Wilson Memorandum to the Secretaries of the Army, Navy and Air Force dated 26 Feb 1953.

* Use of these principles for non-clinical research related to nuclear, biological and chemical warfare defense was promoted before the research programs were planned and funded.

Army Directive CS-385 : Exceeded Nuremberg Code Protections

- Added Consent must be in writing, “volunteer agreement”.
- Jurisdiction & responsibility of Secretary of branch of PI conducting study.
- Use minimum number of subjects for valid outcome. No POW.
- Required additional safeguards.
- Secretary of Army must sign per Surgeons General of Army, Navy, Air Force, and/or USPHS.
- Included an extensive listing of ways DoD could pay for injuries to research subjects.

Cold War Research at Fort Detrick 1954 - 1973



CD-22 Program 1954 – 1956

Operation Whitecoat 1956 - 1973

Multifaceted CD-22 Was Designed to Determine:

- Human vulnerability in realistic BW scenarios.
- Effective prevention and treatment of BW casualties.
- Determination of minimal infective doses.
- Effectiveness of vaccines and drugs.
- Serological responses to infections, and.
- Clinical effects of various doses of infectious agents.

The CD-22 Program Focused on Human Responses to Prototypes:

Q fever and Tularemia were regarded by CES of AFEB as acceptable prototypical BW agents for testing in Humans that satisfied limiting characteristics* of low lethality, no serious chronicity anticipated, effective therapy available and there was adequate animal experimental data on safety and protective efficacy.

**[as described in the Wilson Memorandum cs-385].*

The US Army Medical Unit at Fort Detrick - 1956

USAMU was created in 1954 to develop the means to diagnose, treat and prevent diseases caused by biological warfare agents. The cs-385 regulation for ethical operation, plans for organization of the institute, preparation of protocols and initiation of the first human studies took place within 3-6 months of its creation.

Operation Whitecoat Protocol Review Process

- Medical investigator prepares human use protocol.
- Reviewed at a “Protocol Meeting” attended by Commander, Scientific Advisor, & Division Chiefs.
- Approved protocols forwarded to USAMRDC for further approval by HQDA SGRD-DR. This could entail review by CES of AFEB (before 1972) or HSRRB (after 1973).
- When final approval is given, Whitecoat volunteers are briefed, attend a project interview, and informed consent documents are signed after as much as 4 weeks to as little as 24 hours had passed.

UNITED STATES ARMY MEDICAL UNIT
WALTER REED ARMY MEDICAL CENTER
FORT DETRICK, FREDERICK, MARYLAND 21701

IN REPLY REFER TO
MEDEC-M

30 November 1967

MEMORANDUM FOR RECORD

The following individuals met this date as a committee for the purpose of reviewing volunteer research project No. FY 68-7, "Comparison of Blood Levels and Urinary Excretion of Chloromycetin(R) and a Generic Preparation" submitted by LTC Peter J. Bartelloni:

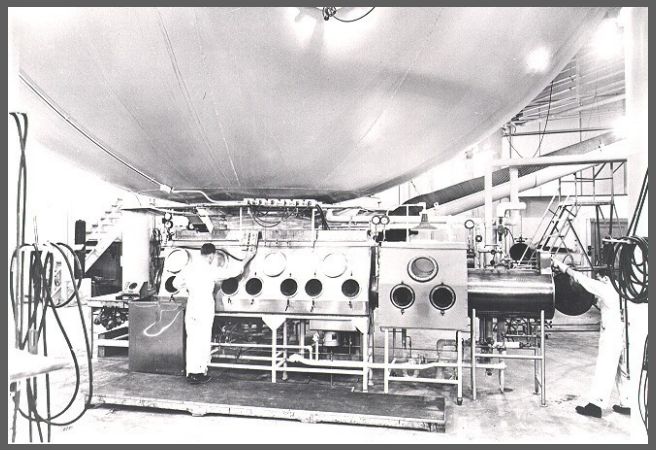
COL William R. Beisel, Acting Commander and Chief, Physical Sciences Division
Dr. Martha K. Ward, Chief, Bacteriology Division
LTC Peter J. Bartelloni, Chief, Medical Division
LTC Stewart McConnell, Assistant to the Commanding Officer and Chief, Animal Assessment Division
Dr. Francis E. Cole, Jr., Acting Chief, Virology Division
CPT Earl J. Wright, Acting Chief, Pathology Division
CPT John L. Winnacker, Medical Division

The committee voted unanimously to approve this project as submitted.

William R Beisel

WILLIAM R. BEISEL
Colonel, MC
Acting Commander

Aerosol Efficacy Studies in 8 Ball



Q-fever and Tularemia were approved for these studies because safety criteria were met and cure was assured.

FDA Historic Milestones

- **1953** Federal Security Agency becomes Department of Health, Education, & Welfare (HEW).
  - Factory Inspection Amendment clarifies previous law and requires FDA to give manufacturers written reports of conditions observed during inspections and analyses of factory samples.
- **1955** The Division of Biologics Control became an independent entity within the NIH, after polio vaccine thought to have been inactivated is associated with about 260 cases of polio.

Moral Dilemma: Comply with FDA law vs Intent to Benefit in BW Emergency

- 1962 Kefauver-Harris drug amendments requiring proof of BW drug efficacy created a moral dilemma.
- Risk killing subjects in a valid clinical trial, versus
- withholding potentially life saving drugs or vaccines because they lacked substantial evidence of human clinical efficacy.

1962 Exemptions to AR 70-25: Double Edged Sword of Definitions

3. Exemptions to AR 70-25 *(26 March 1962).* The following categories of activities and investigative programs are exempt from the provisions of these regulations:

a. Research and non-research programs, tasks, and tests which may involve inherent occupational hazards to health or exposure of personnel to potentially hazardous situations encountered as part of training or other normal duties, e.g., flight training, jump training, marksmanship training, ranger training, fire drills, gas drills, and handling of explosives. *exposure to chemical agent , cabin decompression and A-bomb blast were "training exercises"

b. That portion of human factors research which involves normal training or other military duties as part of an experiment, wherein disclosure of experimental conditions to participating personnel would reveal the artificial nature of such conditions and defeat the purpose of the investigation. *unethical LSD experiments tested vulnerability to espionage.

First DoD / FDA MOU 1964

The 12 May 1964 Memorandum of Understanding

This MOU permitted DoD to use investigational products in classified clinical investigations or non-classified research programs. The term "non-classified research programs" included "ethical medical and clinical investigations involving the basic disease process or new treatment procedures conducted by the Army Medical Service for the benefit of patients." Clinical research with drugs and biologics required submission of an IND application to the FDA.

FDA Historic Milestones

- **1972 Regulation of Biologics** including serums, vaccines, and blood products is transferred from NIH to Food and Drug Administration.
- **1972 Title 10 USC 980** added to Department of Defense Appropriations bill.
  - Informed Consent required for all research including that intended to benefit the patient.
- **1976 Medical Device Amendments** passed to ensure safety and effectiveness of medical devices, including diagnostic products.

USPHS Tuskegee Syphilis Study Scandal of 1972 Led To New Regulations:

- National Research Act of 1974 requiring regulations for protection of human subjects.
  - Informed consent requirements.
  - Review of research by IRBs.
- Created the national commission for the protection of human subjects of biomedical and behavioral research.
- Commission wrote the **“Belmont Report”** in 1979.

Second DoD / FDA MOU 1974

The 24 October 1974 Memorandum of Understanding

This MOU restricted DoD authority to use investigational products for force health protection. Classified clinical investigations could be exempted from the Federal Food, Drug and Cosmetic Act. However, both DoD and FDA would need review and approve use of products in military personnel that were not approved by the FDA but were "tested under IND regulations sufficiently to establish with reasonable certainty their safety and efficacy." All other clinical testing of investigational drugs sponsored

The Common Rule – 45 CFR 46 - 1981

- 1981: DHHS & FDA published convergent regulations based on Belmont principles
- 1991: 17 federal departments & agencies agreed to adopt the basic human subject protections (DoD uses 32 CFR 219)
- All federally sponsored research covered by a common set of protective mechanisms
  - Review of research by an IRB
  - Informed consent of subjects
  - Institutional assurances of compliance

Present DoD / FDA MOU 1987

21 May 1987 Memorandum of Understanding

The most recent MOU executed on 21 May 1987 is still in effect. This MOU requires FDA review for the use of any investigational new drug by the DoD (i.e., No exemptions from the Food Drug and Cosmetic Act). In the case of classified research DoD must submit a "classified IND or IDE application" for review and approval by FDA. FDA is responsible for having reviewers with the security clearance needed to assess these activities.

Ended Exempt status for Special

Moral Dichotomy: Research vs Intent to Benefit in Emergency

- Ability to use products labeled IND to benefit war fighter and laboratory personnel becomes less clear.
- MOUs with FDA (1964 & 1974 through 1987) allowed DoD to exempt from FDA requirements well-studied IND products if they were to be used for treatment.. ***i.e.“intent to benefit” not generation of knowledge.**
- Research with IND products to discover new treatment uses and meet requirements for New Drug Application rigorously followed DoD and FDA requirements.

Today's Situation 1987-now

- New FDA requirements in 1997, 1999 and 2002 introduced more stringent and inflexible IND requirements making DoD compliance virtually impossible in contingency operations.
- IND products cannot be used by DOD except in strictly regulated clinical research trial format conducted in compliance with IND and good clinical practices [GCP] requirements, irrespective of "intent to benefit".

Today's Situation What's New?

- The "investigational" label and structured research format interferes with subject acceptance of products because of perception of experiment when treatment is intended.
- Difficulties meeting IND/GCP regulatory requirements may cause DoD to deviate from FDA requirements or fail to successfully accomplish force health protection.
- Must Seek "Streamlined IND" for rapid Licensure of advanced products with utility or potential utility.
- Emergency Use of Key FDA-Unapproved Drugs becomes possible for "pipeline" products via Project BioShield.

DoD Use of Project BioShield

- **BioShield:** Establishes an FDA Emergency Use Authorization for critical biomedical countermeasures. FDA may approve solely for emergency use a product not approved for full commercial marketing.
  - **Passed: H.R. 2122—Project Bioshield Act of 2003.**
  - **Pending: S. 15 Project BioShield Act of 2003 and the Biodefense Improvement and Treatment for America Act.**
- DoD may use BioShield procedures for Force Health Protection if legislation approved.
- This legislation resolves the ethical dichotomy and dilemma that DoD has had since the 1987 MOU.

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